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Review Article

miRNA for Cancer Treatment

New Developments in Cancer Treatment Using miRNA Manipulation

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Abstract: MicroRNAs (miRNAs) constitute a subclass of short non-coding RNA used throughout cells to control gene expression. Usually, 22 nucleotides long, just one miRNA can control the transcription of many genes. The previous ten years have observed new prospects for diagnosing and treatment advancement due to studying miRNA biology about cancer. While miRNAs are crucial in phenomena such as genomic instability, aberrant transcriptional control, altered epigenetic regulation, and deficiencies in the biogenesis devices, microRNA dysregulation is frequently linked to cancer. Whenever changed, microRNAs can control oncogenes or tumor suppressor genes, which can influence the emergence of tumors. More research is fundamental to confirm the viability of such approaches via means of miRNA, and its assessment has increased avenues for using miRNAs as possible biological cancer markers and treatment objectives. Our review concentrates on how miRNAs control tumor expansion and the possible uses of miRNA regulation in cancer treatment. MiRNAs can be utilized as powerful therapeutic agents due to their propensity to focus on multiple oncogenes and tumor suppressors. Furthermore, miRNA profiling studies provide new details regarding the molecular mechanisms of cancer and could be an early detection tool for cancer. miRNAs are being investigated for their potential to reduce drug resistance and toxicity and improve the efficiency of existing cancer treatments. Thus miRNA-based strategies provide the potential to aim specific cancer cells, making them potentially valuable for personalized medicine approaches. Our review focuses on the regulatory mechanisms of miRNA, biogenesis, biosynthesis, Gene amplification, Cancer Biomarkers, and cancer stem cells.

Keywords: miRNA, biogenesis, micro RNA Dysregulation, Gene Amplification, and Cancer Stem Cells

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1. INTRODUCTION

MicroRNAs (miRNAs) are short non-coding RNAs that control the subsequent process of gene declaration. They are generally 20–22 nucleotides long and intrinsic to cell [1]. The transcriptional activation of oncogenes regulates various biological activities, including cancer. By locating an additional area in the 30 Untranslated Region (UTR), miRNAs influence a wide range of biological activities, including the division of cells, proliferation, and death, through feedback mechanisms. Since miRNAs are incredibly preserved throughout all spheres of life, likely, miRNAs function post-transcriptionally as broader regulators. It suggests they can regulate many genes and pathways, making them attractive targets for therapeutic intervention. Thus, miRNAs are being investigated as promising tools for treating illnesses like cancer. This research has proven that miRNAs play a significant part in regulating biological processes through their precise interactions with proteins, transcription factors, proteins, and RNP complexes. In addition, it was revealed that the mutations in mir-15 and mir-16-1 decrease cancer growth by hindering the bcl-2 protein and triggering apoptosis. [2] This is important because when miRNAs bind to proteins or transcription factors, they can alter their declaration and function. By manipulating the declaration of these proteins, miRNAs can impact the cell cycle, cell survival, and cell differentiation. For example, if the mutations in mir-15 and mir-16-1, they uncovered to inhibit the declaration of the bcl-2 protein, which is known to participate in the control of apoptosis[3]. Thus, these mutations can potentially reduce cancer growth by triggering apoptosis. Our miRNAs' abilities for cancer detection, categorization, evaluation, and prediction have considerably improved with the innovation of DNA sequencing and miRNA profiling techniques[4]. It subsequently helps to provide a more customized and accurate treatment plan for each cancer patient. Furthermore, miRNA profiling can be used to distinguish biomarkers for diagnosis and prognosis of tumors and monitor cancer's response to treatment. MiRNA profiling can also be applied to identify potential therapeutic targets and evaluate the efficacy of potential drugs.

1.1 Biogenesis, Biosynthesis, And Regulatory Mechanisms of miRNA

miRNA s are developed in an extremely consistent manner. miRNA s are incorporated into the human genome in diverse ways, including with several antecedents and expressions from intergenic transcripts, each of which only encodes one strand of premiRNA (which later takes on an additional structure like a hairpin) [5]. RNA polymerase II does most pri-miRNA transcription, although RNA polymerase III also does part of it. When pri-miRNA enters the nucleus, RNA-binding proteins DGCR8 and DROSHA, a type III RNase, act as endonucleases to cleave the newly synthesized pattern into an eighty to one hundred nucleotide long pre–miRNA sequence. The pre-miRNA is exported through the cell membrane to its core by the Ran/GTP/Exportin-5 complex. The pre-miRNA is broken down into a grow-up, double-stranded miRNA strand in the cytoplasm by the cytoplasmic ribonuclease (RNase III) enzyme Dicer. This processing technique amplifies mature separate-strand miRNA, which binds to Argonaute 2 (AGO2) to form the RNA-induced silencing complex (RISC). This complex can inherently bind the cytosolic mRNA targets of this complex's usual 30 UTRs. The similarity between the base-pairing at the 50 ends of mature miRNA is the basis for interaction with mRNAs. The miRNA may target a diverse array of various mRNAs because of the interaction site's modest length. miRNA functions as a receptor in cancers, increasing a wide range of communication systems. Modifying a nuclear factor-kB signaling pathway revealed that miRNAs impacted Toll-like receptors in killer cells that are natural[6-8].

1.2 miRNA's Activity in Cancer

miRNA s have become known in recent years as a unique cell element that behaves differently in sick and healthy cells. Potential miRNA-based biomarkers for cancer discovered in various bodily fluids enable easier diagnosis and surveillance. miRNAs are small non-coding RNAs that can regulate gene expression and be dysregulated in many disease states, including cancer. By detecting nearby certain miRNAs in a patient's bodily fluids, it could be possible to indicate the nearby cancerous cells without having to perform a biopsy or other invasive procedure by investigating the "tumor microenvironment [9]." Tumours of diverse sorts have distinctive miRNA signatures that aid in the classification of various kinds of cancer. To regulate genes, miRNAs primarily perform two tasks: (1) the highly cell-type dependent homeostatic control of gene regulation; and (2) the establishment of cell destiny and the ongoing preservation of cell identity via feedback mechanisms. MiRNAs act as on/off switches for genes, so they can turn on or off certain genes in a cell by binding to the mRNA that codes for that gene. It allows miRNAs to control the proteins of key molecules that participate in the creation and upkeep of the tumor microenvironment, which can influence tumor growth and progression. The initiation and repression of the AMP-activated protein kinase pathway control cell survival and mammalian target of rapamycin-activated cell proliferation[10]. Tumour cells lose the ability to regulate mRNA via microRNA during mRNA translation due to genetic changes, single nucleotide polymorphism, and 30 UTR ablation. The overall amount of mature miRNA in the cell is significantly decreased due to polymorphisms that decrease the effectiveness of the miRNA interpreting mechanism. It may end in the overexpression of certain mRNAs, which may end in the proliferation and spread of cancer cells. miRNA biosynthesis and regulation are shown below in Figure 01.

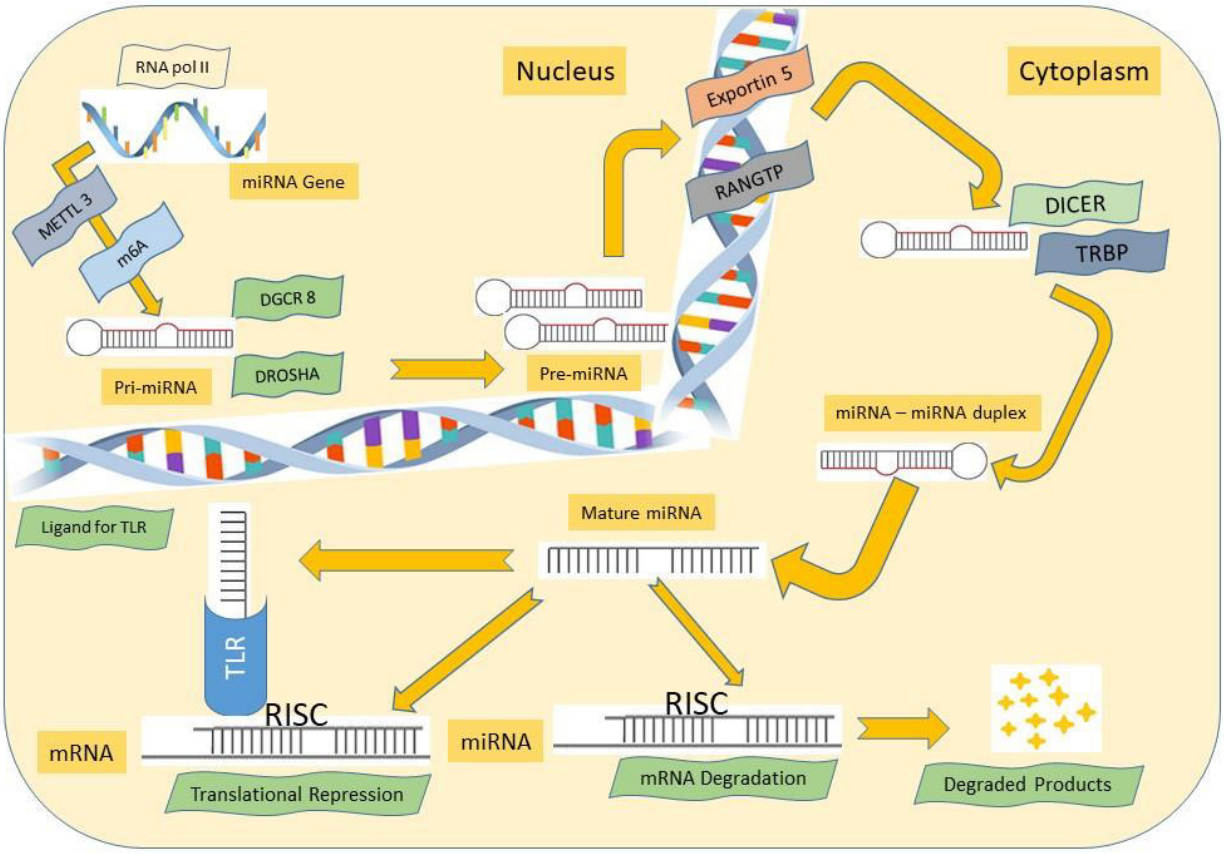

Fig 1: miRNA biosynthesis and regulation

1.3 Gene Amplification / Deletion That Affects the miRNA

miRNA expression levels are assumed to have changed in cancerous cells, and the outcome is gene amplification, loss, or translocation. For instance, lung cancer and B-cell lymphomas exhibit gene amplification for miR-17-92 clusters. In place of this, the 13q14 chromosome exhibits a decrease of miR-15a/16-1-related genes in B-cell CLL patients. Regarding those who have lung cancer, the 5q33 area shows the presence of miR-143 and miR-145[11-13]. According to whole-genome sequencing of these samples, many miRNA genes are situated in tumor-associated genomic regions, such as tumor regulator genes, oncogenes, or frequent discontinuity areas. The outcome is that some particular genomic locations deleted, amplified, or moved are to blame for the changed miRNA structures. It can disrupt gene regulation and lead to cell transformation and tumor development. Therefore, understanding the role of miRNA in this procedure might result in the creation of more effective treatments for lung cancer. Furthermore, by understanding how miRNA is affected by structural modifications in the genome, it may be possible to develop targeted treatments that can restore normal gene regulation and reduce the possibility of tumor progression. It could lead to more effective treatments with fewer side effects.

1.4 Erroneously Epigenetic Modification

Cancer cells exhibit atypical epigenetic alterations such as global DNA hypo-methylation, diversity in altering histone patterns, and hyper-methylation of tumor inhibitory genes. In T24 urinary cancer cells subjected to acetylation of histone and DNA methylation inhibitors, 17 miRNAs showed a greater than threefold increase in expression[14]. Since miR-29 expression inhibits the formation of DNMT3A and DNMT3B, genes necessary for controlling DNA methylation, it has been demonstrated that the miRNA and epigenetic strategies have a significant association with cancer. Therefore, epigenetic strategies, such as miRNA expression, appear to be important in establishing and progressing urinary cancer. This association between miRNA expression and epigenetic processes is due to DNMT3A and DNMT3B's ability to control the methylation of genes, which has been linked with an outbreak of cancer[15]. The fact that miR-29 expression inhibits the making of these proteins suggests that the miRNA and epigenetic processes directly affect the making and outcomes of urinary cancer.

1.5 Inconsistencies in the Mechanism that Produces miRNA

The malfunctioning of substrates and enzymes in the biological routes, such as Dicer, Drosha, DGCR8, and exportin 5, strongly impacts the total competent miRNA levels. For example, Dicer1 and Drosha's partial deletion brought about quicker carcinogenesis in various kinds of cancer, as demonstrated in both in-vitro and in-vivo models[16]. It is because miRNA biogenesis requires endonucleolytic fragmentation of several enzymatic processes, 5' phosphate capping, 3' polyadenylation, and nuclear export. Dicer and Drosha are culpable for the endonucleolytic cleavage step. When either malfunctioning, the following steps are disrupted, and the total competent miRNA levels are reduced, leading to quicker carcinogenesis[17]. This disruption to the miRNA biogenesis

process can lead to an increased rate of carcinogenesis, making it vitally important that Dicer and Drosha function correctly.

1.6 Tumors with Aberrant Levels of miRNA

The capacity to evade growth inhibitors, sustain proliferative signaling, boost immortality by recombination, stimulate angiogenesis, and start spreading via metastasis are all acquired by tumors. It is thought that dysregulated miRNAs operate in the form of inhibitory genes or oncogenes based on the gene objective, influencing a single of the mentioned previously hallmarks. miRNA profiling of various malignancies has shown abnormal levels compared to normal tissues. It has evolved clear from several research that miRNAs are infused into a diversity of cell cycle routes, maintaining proliferation and avoiding slowing down growth in malignant cells[18]. It allows tumor cells to escape the common apoptotic pathways and evade senescence. Furthermore, Tumour cell growth and dissemination are caused by angiogenesis and invasion, which can be modulated by dysregulated miRNAs[19]. As such, miRNAs play a crucial part in the onset and spread of cancer, and understanding their behavior is essential to understanding cancer itself.

1.7 Concentrating on Cancer Stem Cells

According to the biological investigation, fragile sites include oncogene-specific miRNAs that are vulnerable to losing or decreasing miRNAs, which subsequently causes several oncogenes to be enhanced. These modifications impact cancer-related activities, including metastasis, anti-apoptotic, tissue encroachment, and treatment resilience. A particularly efficient mode of therapy is cell-based targeted administration of miRNA inhibitors or miRNA mimics. Therefore, miRNAs serve as the physiological indicators of Cancer stem cells(CSC), and more research may disclose the crucial part of miRNAs in CSCs, particularly in diagnosis, prognosis, and therapy. It would improve the present cancer treatment protocol and minimize side effects.Furthermore, miRNAs can trace CSCs in the body and monitor the potency of cancer treatment. Therefore, understanding the part of miRNAs in cancer can help researchers develop new and more effective therapies. miRNAs offer a unique opportunity to target CSCs specifically, as CSCs often express miRNAs that are not expressed in normal cells, offering a viable adversary for therapeutic intervention. By targeting these miRNAs, it would be possible to selectively target stem cells and potentially eradicate them without damaging normal cells, thus providing a more effective and safer cancer treatment[20]. Consequently, targeting miRNAs could provide a new way to selectively target CSCs, eliminating them without harming healthy cells, which could lead to more effective and safer cancer treatments.

1.8 Cancer Biomarker Identification miRNA

Highly stable in bodily fluids, microRNAs are believed to be linked to cancer survivors' outcomes or treatment reactions through a variation in expression. Circulating miRNAs are released into the environment by tumorous tissue and are shielded against internal RNase function. This protection enables them to be present among the tissues, such as in blood specimens, where they can be monitored for changes. These changes in expression can be used to determine how a patient respond to treatment and predict the outcome of their cancer. Cancer detection and outlook are made easier by analyzing several floating miRNAs, which also help identify different tumor groups. Exosomes contain an abundance of micro-RNAs, which gives them resilience and is essential for the growth and spread of cancer[21]. By analyzing the varying degrees of verbalization of the floating miRNAs, researchers can determine the type of cancer, its stage, and its prognosis. It helps physicians to tailor treatment plans for each patient and make better-informed decisions about their care. Exosomes also allow for a better understanding of how cancer spreads, which is useful for new treatments and enhancing existing ones. Utilizing blood, plasma, and bodily fluids, many cancer-specific miRNAs encapsulated in exosomes (30-120 nm membrane-derived vesicles) have been detected, offering a quick and accurate way to diagnose cancer. For example, exosomal has-miR-933, produced from gastric juice, was implicated in functional dyspepsia[22].

1.9 Medical Procedures for Cancer Comprised of miRNA

The replication of tumor-suppressive miRNAs declines due to cancer growth, advancing the oncogenic signaling pathway. Therefore, it makes sense to resupply the miRNAs that restrict cancer growth at the tumor's location. It can be done by utilizing miRNA gene therapy, which involves using miRNAs to target genes involved in cancer growth and invasion. Inspired by miRNA, gene therapy has been demonstrated to reduce tumor growth in animal models[23] effectively. As a replacement, oncomiR-dependent cancers are targeted using miRNA antagonists (antimiRs). In targeting the stromal cells supporting cancer growth, miRNAs also engage the endothelial and fibroblast cells that limit angiogenesis and fibrosis[24]. AntimiRNAs can slow the progression of tumors by narrowing down the signaling pathways that regulate tumor creation and limiting the growth of new vessels, which bring nutrients to the tumor and prevent fibrosis, and can lead to further tumor growth. Therefore, the characteristics of the miRNA lead play a significant part in creating the miRNA antagonist or mimic. It is why targeting miRNA pathways can be a powerful and potentially less invasive way to fight cancer.

1.10 Classifying the Reasoning for Intended miRNA

Two key factors that support the application of miRNAs as anticancer agents are that miRNA expression is dysregulated in cancerous cells relative to normal tissues[25], and miRNA expression may be targeted to alter the cancer phenotype. The capacity of miRNAs to target many genes, usually in the framework of a network, makes them particularly attractive as medicines since they are so effective at controlling various biological functions that are important for both healthy and cancerous cell homeostasis. By selectively attacking a series of phosphatases, miR-181 has been demonstrated to be essential for controlling T cell receptor accessibility and signaling potency at the post-transcriptional stage[26]. Carcinogenesis typically affects the cell cycle, cell adhesion, chromosomal stability, and pathways for fixing DNA. It is logical to assume that miRNAs play important functions in orchestrating malignant networks due to their control over several pathways and coordinate actions in healthy normal cells and tissues. One might consider miRNAs a "power grid" connecting all these proteins and transcriptional networks. Focusing on specific genes or proteins might not be as

effective or as extensive as establishing therapeutic ways to alter the production of miRNA and restore equilibrium.

1.11 Techniques for Treatments Based on miRNA

Targeting miRNA activity in cancer involves two primary approaches: stopping the production of an oncogenic miRNA or compensating for the missing tumor-fighting miRNA; direct techniques utilize oligonucleotides or virus-based structures[27]. These techniques can either block the miRNA from binding or act as decoys to the miRNA, preventing it from binding to its target. Alternatively, indirect techniques employ antagomirs and miRNA sponges to target miRNA activity[28]. The indirect approach uses medications focusing on miRNA synthesis and processing to modify miRNA expression.

1.12 Sponges for miRNA.

MiRNA sponges are transcripts generated from mammalian manifestation vectors with several important tandem-binding sites for a specific miRNA. miRNA sponges voyage to the miRNA of interest and prevent it from combining with its target mRNA, thereby reducing the manifestation of the intercept gene[29]. This approach allows for a more focused modulation of miRNA frequency and a more powerful strategy than direct miRNA inhibition. MiRNA sponges can be designed to target a specific miRNA with high affinity, thereby preventing it from binding to its intercept mRNA and thus reducing the frequency of the intercept gene[30]. This method is advantageous compared to direct miRNA inhibition because it is more precise and could be used to control specific gene expression pathways. Moreover, miRNA sponges can be engineered to achieve greater levels of miRNA knockdown, further enhancing the efficacy of miRNA regulation.

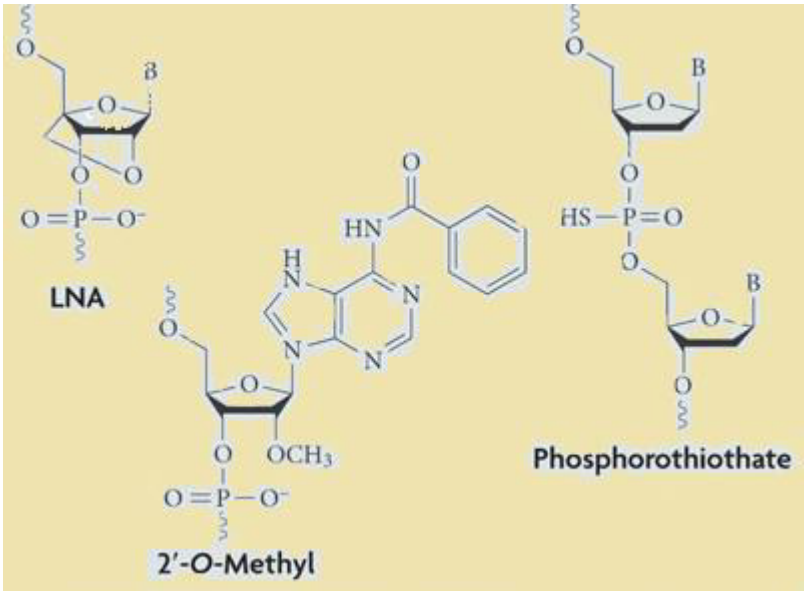

Fig 2: Patterns of oligonucleotide substitution that are often used. Laminated nucleic acid (LNA), 2′ -O-methyl, and phosphorothiolate101,107 are three of the prevalent oligonucleotide-altering patterns[31].

1.13 Obstacles with miRNA-Based Interventions

The need for tissue-specific distribution and cellular absorption of enough synthetic oligonucleotides to enable persistent goal blockage constitutes one of the main challenges for applying miRNA therapies in vivo. Current delivery strategies for miRNA therapies are unsuitable for in vivo applications due to their lack of safety and efficiency. Therefore, the progression of new delivery systems is necessary to apply miRNA therapies in vivo successfully. The biological instability of these substances in human fluids or tissues is the initial hurdle to be addressed since unaltered 'naked' oligonucleotides are quickly broken down by cellular and serum nucleases[31]. Researchers have explored delivery systems, including cationic liposomes, micelles, polymers, and peptides, to overcome this issue. These can protect and stabilize the oligonucleotides while allowing them to enter the target cells.Additionally, these delivery systems also have the potential to target specific cell types, thus increasing the efficiency of the therapy. However, oligonucleotides have an opposite charge and are large, and they may have trouble entering cells because of the second barrier—poor cellular absorption. To combat this, oligonucleotide modifications have been designed to boost cellular delivery, including cationic lipids and polyethylene glycols.

2. CONCLUSION

Subsequently, it was discovered that the deletion of miRNAs was associated with CLL; researchers worldwide have been examining the function of miRNAs in various cancers and why miRNA expression is dysregulated. It demonstrated the function of many processes, including altered miRNA synthesis, epigenetic factors, aberrant regulation of gene transcription, and miRNA gene deletion or amplification. Although miRNAs have a wide range of potential targets, they are believed to cause tumors by changing specific targets and acting as an oncogene or a tumor suppressor. Several miRNA inhibitors and miRNA mimics are being studied in the clinic with the potential to be used therapeutically. In addition, research is being done on the function of noncoding RNAs, such as circular and long noncoding RNAs.

3. CONFLICT OF INTEREST

Conflict of interest declared none.

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